REMARKS

Claim amendment

Claim 16 has been amended to more clearly indicate that the immune response to the T-cell independent antigen is enhanced in the host, compared to an existing immune response to the T-cell independent antigen in the host. Support for the amendment can be found, for example, on page 5, lines 5-6 of the specification.

Rejection of Claims 16 and 36-41 under 35 U.S.C. §112, second paragraph

Claims 16 and 36-41 are rejected under 35 U.S.C. §112, second paragraph "as being incomplete for omitting essential steps" (Office Action, page 2). The Examiner states that the "omitted steps are: what is compared to determine whether the immune response to a T-cell independent antigen is enhanced in a host.

As indicated above, Claim 16 has been amended to more clearly indicate that the immune response to the T-cell independent antigen is enhanced in the host, compared to an existing immune response to the T-cell independent antigen in the host, thereby obviating the rejection.

Rejection of Claims 8, 16, 20, 24 and 30-45 under 35 U.S.C. §112, first paragraph

Claims 8, 16, 20, 24 and 30-45 are rejected under 35 U.S.C. §112, first paragraph "as failing to comply with the enablement requirement" (Office Action, page 2).

Specifically, the Examiner states that the "specification only discloses effect of co-administration of IL-12 protein and TI antigen in stimulating or enhancing immune response to the TI antigen in a host but fails to provide data regarding whether co-administration of a TI antigen and a polynucleotide or vector encoding IL-12 protein can stimulate or enhance immune response to the TI antigen in a host" (Office Action, page 5 and page 8). The Examiner further states that there is "no evidence of record that administration of a TI antigen and a polynucleotide or vector expressing IL-12 protein to a host via various administration routes would result in sufficient expression of IL-12 protein at target site so as to provide therapeutic effects" (Office Action, page 6).

Applicants respectfully disagree. In the specification as filed, Applicants show that administration of IL-12 protein and a TI antigen (*e.g., S. pneumoniae*; *N. meningiditis*) induce or

enhance an immune response to the antigen *in vivo* (specification, page 13, line 25 - page 21, line 10). Applicants further teach that "the IL-12 and/or TI antigen can be administered by *in vivo* expression of polynucleotides" and provide adequate guidance to one of skill in the art for doing so (specification, page 8, lines 4-21). In addition, in the previously filed responses mailed to the U.S. Patent Office on September 29, 2003 and December 7, 2004, Applicants have provided numerous references (*i.e..,* Exhibits A-F) as evidence that the state of the art for IL-12-based gene therapy was not unpredictable at the time of Applicants' invention, and undue experimentation is not required for one skilled in the art to practice the full scope of Applicants' claimed invention. Thus, the guidance Applicants provide in the specification as filed in combination with the knowledge possessed by one of skill in the art at the time of Applicants' invention is more than enough evidence that administration of a TI antigen and a polynucleotide or vector expressing IL-12 protein to a host via various administration routes (*e.g.,* vectors expressing IL-12; naked DNA) would result in sufficient expression of IL-12 protein *in vivo* so as to provide the claimed therapeutic effects.

Discussing Exhibits A-F, the Examiner states that "the prior art only teaches intradermal or intramuscular injection of IL-12 DNA into a host to stimulate cell-mediated immune response, however, none of the references teach that introduction of IL-12 DNA into a host other than intradermal or intramuscular injection can stimulate or enhance immune response, or injection of IL-12 DNA can stimulate or enhance humoral immune response in a host" (Office Action, page 6 and page 9).

However, in the specification as filed Applicants have shown that administration of IL-12 protein and a TI antigen induce or enhance an immune response, such as a humoral immune response, to the TI antigen *in vivo*. Applicants also teach that the claimed methods of inducing or enhancing an immune response to a TI antigen in a host can be carried out wherein the IL-12 is administered as a polynucleotide under conditions in which the IL-12 is expressed *in vivo*. Exhibits A-F were provided to show that at the time of Applicants' invention, one of skill in the art knew how to prepare and administer a polynucleotide expressing IL-12 in combination with an antigen to induce an immune response to the antigen. Furthermore, it is not required for patentability that Applicants show that "introduction of IL-12 DNA into a host other than

intradermal or intramuscular injection can stimulate or enhance immune response" in a host (Office Action, page 6 and page 9). As noted in the MPEP:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569,1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling) (MPEP, 8th ed., August 2001, section 2164.08(c), page 2100-199).

Clearly, based on the art of record (Exhibits A-F), a skilled person could determine which embodiments of preparing and administering a polynucleotide expressing IL-12 under conditions in which the IL-12 is expressed *in vivo* that were conceived (*e.g.,* vectors expressing IL-12 DNA; naked IL-12 DNA), but not yet made, would be inoperative or operative by reading relevant articles that were published at the time of Applicants' invention (*e.g.,* Tahara *et al.* (Exhibit A), Rakhmilevich *et al.* (Exhibit B), Kim *et al.* (Exhibit C), Okada *et al.* (Exhibit F)), which is an "expenditure of no more effort than is normally required in the art."

Referring to the Kim *et al.* reference (Exhibit C), the Examiner states that "[i]t appears that the type and level of Ab response can vary with the combination of a DNA vaccine (DNA for HIV-1 Ag) and different expression plasmids expressing different proteins (IL-12 or GM-CSF), and codelivery of IL-12 gene and DNA vaccine results in reduction of specific Ab response but dramatic increase in specific CTL response" (Office Action, page 7). Referring to the Okada *et al.* reference (Exhibit F), the Examiner states that "[i]t seems that co-administration of IL-12 expressing plasmid and DNA vaccine for HIV-1 does not increase or enhance humoral immune response in mice as compared to HIV-1 DNA vaccine alone" (Office Action, page 7). In a later discussion of the Kim *et al.* and Okada *et al.* references, the Examiner states that "[i]t seems that co-administration of IL-12 expressing plasmid and DNA vaccine for HIV-1 does not increase or enhance humoral immune response in mice as compared to HIV-1 DNA vaccine alone" (Office Action, page 10).

Applicants fail to see how the immune response observed by Kim *et al.* or Okada *et al.* is relevant to Applicants' claimed invention. The Kim *et al.* reference (Exhibit C) reference and the Okada *et al.* reference (Exhibit F) relate to the immune response associated with the administration of vectors expressing IL-12 ***and/or GM-CSF***, and a ***T-cell dependent antigen of HIV***. Indeed, later in the Office Action, the Examiner notes Applicants' citation of Okada *et al.*, and states that "Okada use the combination of a polynucleotide expressing IL-12 protein and a DNA vaccine for HIV-1, ***however, the present invention is directed to the combination of a polynucleotide expressing IL-12 and a TI antigen*** (Office Action, pages 9-10). As noted above, Exhibits A-F were provided to show that at the time of Applicants' invention, one of skill in the art knew how to prepare and administer a polynucleotide expressing IL-12 in combination with an antigen to induce an immune response to the antigen *in vivo*.

It is the Examiner's opinion that "it would be unpredictable whether codelivery of various TI antigens and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response. It also would be unpredictable whether codelivery of various TI antigen and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response, in vivo via administration routes other than intradermal and intramuscular injections, for example oral administration, intravenous administration, or intraperitoneal injection. The specification must provide sufficient enabling disclosures for the full scope of the invention claimed but fails to do so" (Office Action, pages 7 and 9). Referring to the Kim *et al.* (Exhibit C) and Okada *et al.* (Exhibit F) references, the Examiner further states that "[i]t appears that gene delivery to a host to stimulate an immune response needs to be considered individually and the result of one gene delivery can not be extrapolated into success for another gene delivery in vivo" (Office Action, page 10).

Applicants respectfully disagree. Exhibits A-F all report that administration of a polynucleotide expressing IL-12 induced an immune response *in vivo* using, for example, a plasmid and naked DNA. Applicants are also confused by the Examiner's statement that "[i]t also would be unpredictable whether codelivery of various TI antigen and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response, in vivo via administration routes other than intradermal and intramuscular

injections, for example oral administration, intravenous administration, or intraperitoneal injection". ***Is the Examiner suggesting that in order to be provide an enabling disclosure, Applicants must show that administration of a polynucleotide expressing IL-12 and a TI antigen via any route of administration will induce all types of immune responses to a TI antigen in vivo to be enabled for the full scope of the invention?*** As noted above, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. Clarification of the Examiner's position is respectfully requested.

The court has clearly stated that:

> Enablement is not precluded by the necessity for experimentation such as routine screening... However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'... The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness having due regard for nature of the invention and the state of the art... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (*In re Wands*, 1400 U.S.P.Q.2d 1400, 1404 (CAFC 1988)).

In *Wands* case, which related to monoclonal antibody technology, the court stated that:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. . . Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics (*In re Wands*, 1400 U.S.P.Q.2d 1400, 1406 (CAFC 1988)).

Thus, a considerable amount of experimentation is permissible if, as here, it is routine. *Clearly, the court recognized that practitioners of the art could not **predict** which hybridomas would be negative, and that **screening** of hybridomas to determine which hybridomas were negative and which hybridomas were positive, which entails time consuming in vivo experiments (e.g., immunizing animals with myeloma cells to make hybridomas), is **routine** to those of skill in the art.*

In the subject application, Applicants have provided a reasonable amount of guidance with respect to the use of an effective amount of interleukin-12 and a T-cell independent antigen, wherein the interleukin-12 is administered as a polynucleotide under conditions in which the interleukin-12 is expressed *in vivo* to induce an immune response to the T-cell independent antigen in the host. Exhibits A-F clearly establish that at the time of Applicants' invention one of skill in the art could prepare and administer a polynucleotide expressing IL-12 under conditions in which the IL-12 is expressed and an immune response is induced *in vivo*. The guidance provided in Applicants' disclosure (specification, pages 13-21) and the state of the art as evidenced in Exhibits A-F also establish that assessing whether administration of an effective amount of interleukin-12 and an antigen (*e.g.*, a T-cell independent antigen), wherein the interleukin-12 is administered as a polynucleotide under conditions in which the interleukin-12 is expressed generates an immune response to the antigen, although time consuming, can be performed without undue experimentation using Applicants's disclosure and routine skills. Given the state of the art, the guidance in the specification, and detailed examples regarding the claimed method, it would not require undue experimentation to make and use the invention as claimed.

Undue experimentation is not required to practice Applicants' claimed invention. Using the guidance provided by Applicants in the specification as filed and the knowledge in the art, a person of skill in the art is fully enabled to administer to a host an effective amount of interleukin-12 and a T-cell independent antigen, wherein the interleukin-12 is administered as a polynucleotide under conditions in which the interleukin-12 is expressed *in vivo* to induce an immune response to the T-cell independent antigen in the host. Furthermore, using routine experimentation and the guidance Applicants provide in the specification, one of skill in the art can assess whether administration of an effective amount of interleukin-12 and a T-cell independent antigen to a host, wherein the interleukin-12 is administered as a polynucleotide under conditions in which the interleukin-12 is expressed in the host generates an immune response to the TI antigen.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

Anne J. Collins
Registration No. 40,564
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: August 8, 2005